

Review Article

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Hepatitis B Reactivation in Patients with Hematological Malignancies and Stem Cell Transplantation

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Abstract

Hepatitis B infection is the leading cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma and is thought to be responsible for million deaths per year globally. Management of patients with resolved or active hepatitis B and cancer is a challenge and these patients are at higher risk of hepatitis B related complications due to immunosuppression and loss of prior immunity. The treating hematologist needs to understand the biology of this common virus, its potential for long-term harm, the necessary laboratory monitoring for their identification and characterization, and the pharmacological interventions for their control. This review offers a general approach to prevention and treatment of hepatitis B reactivation in patients with hematological malignancies and transplant recipients. Practitioners are also encouraged to seek advice and consultation from experts in the design of specific protocols for screening, monitoring and prevention.

Keywords: Hepatitis B; Immunochemotherapy; Reverse Seroconversion; Rituximab; Transplantation

Introduction

Over 350 million people worldwide are chronically infected with Hepatitis B Virus (HBV); the leading cause of chronic hepatitis, cirrhosis and Hepatocellular Carcinoma (HCC) and is responsible for one million deaths per year [1-3]. The prevalence has declined significantly due to the availability of vaccines in the developed world; however it is still prevalent among the immigrant population endemic to this virus. The burden of HBV in the United States is much lower, but it is still estimated to cause chronic infection with approximately 5000 deaths annually from the sequelae of acute and chronic liver disease [3].

Hepatitis B is a small, partially double-stranded, non-enveloped DNA virus. It matures to a covalently closed circular DNA in the nucleus and can persist in a latent state after resolution of viremia [3]. The likelihood of developing a chronic infection after initial infection is high in neonates and immunocompromised individuals but 5% or less in immunocompetent adults. The intensity of acute liver injury from the viral infection relates to the strength of the immune response. Thus, a healthy adult with a robust immune response to the virus may die of fulminant hepatitis after initial infection while demonstrating low viral titers in the blood. An immunocompromised individual, by contrast, may have little laboratory evidence of liver injury, despite displaying high titers of virus in liver and blood. Patients with serological markers showing cleared hepatitis B infection are at risk of reactivation of the virus when they are immunosuppressed. This phenomenon has been most frequently described after allogeneic stem cell transplantation (allo-SCT) and/or the use of certain cancer chemotherapeutic agents [4-7].

Serological Markers for Hepatitis B Virus

The presence of hepatitis B surface antigen (HBs-Ag) is indicative of infection (acute or chronic). Patients who receive vaccination against hepatitis B exhibit antibodies to hepatitis B surface antigen (anti-HBs Ag). The hepatitis B core antibody (anti-HBc) emerges during an infection (IgM is positive during an acute infection and disappears in the chronic phase). In a patient with HBs Ag negative and anti-HBc positive is suggestive of recovery from an acute infection, chronically

infected patient with undetectable levels of HBs Ag, or patients who are distantly immune with undetectable level of anti-HBs in serum (CDC guidelines).

Although reactivation of HBV is mainly found in HBs Ag-positive patients, it can be observed in serologically recovered anti-hepatitis B core antibody (HBc)-positive, HBs Ag-negative patients. Serum HBV DNA typically increases during immune suppression, followed by a disease flare and HBV DNA clearance following immune restoration after immune suppression is stopped [1,2].

Hepatitis B Reactivation after Immunochemotherapy

Risk of reactivation

Reactivation of resolved HBV infection is termed Reverse Seroconversion (RS). Hepatitis B reactivation is a potentially fatal complication in patients receiving high dose chemotherapy. If recognized early and patients are screened appropriately, this can largely be prevented.

In the past decade, the use of rituximab therapy has revolutionized the treatment of lymphoma. The widespread use of cytotoxic chemotherapy and immunosuppressant therapy has resulted in reactivation of HBV resulting in a major health concern [8]. Recent data suggests that rituximab and other monoclonal antibody therapy increases the risk of viral mediated (hepatitis B) complications. In a study of 70 patients with either chronic or past HBV infection as assessed by HBs Ag and anti-HBc, six patients (7.6%) experienced reactivation, three died of liver failure [9,10]. HBs Ag seropositivity was

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an independent risk factor for HBV reactivation. This study suggests that HBV reactivation can occur in patients with past as well as chronic HBV infection during and after rituximab therapy [11]. In a study by Yeo et al. [12] HBV reactivation rate in patients treated with rituximab-containing chemotherapy was compared with the rate in patients treated without rituximab. Among 104 CD20(+) DLBCL patients, 80 were HBs Ag negative. Of the later, 46 patients (44.2%) were HBs Ag negative/anti-HBc positive; 25 of these patients were treated with CHOP chemotherapy regimen and none had HBV reactivation. Among the 21 patients treated with R-CHOP, five developed HBV reactivation, including one patient who died of hepatic failure. Exploratory analysis identified male sex, absence of anti-HBs, and use of rituximab to be predictive of HBV reactivation. In patients with HBs Ag-negative/anti-HBc-positive DLBCL patients treated with R-CHOP, 25% developed HBV reactivation. Therefore, close monitoring after anticancer therapy (especially after rituximab based therapy) is recommended [12].

In an attempt to determine the rate of HBV reactivation in patients who received rituximab-containing combination chemotherapy without concomitant antiviral prophylaxis Koo et al. studied 62 HBs Ag negative/anti-HBc positive patients with B-cell lymphoma treated with rituximab-based immunochemotherapy. Two patients developed HBV reactivation; both were above 70 years of age, received R-CHOP chemotherapy and were negative anti-HBs (surface antibody) at baseline. The overall reactivation rate in this cohort of patients was 3%. The elderly patients, particularly those without anti-HBs, seemed particularly at an increased risk [8].

In a meta-analysis of hepatitis B reactivation in patients treated with rituximab, 971 adult patients were included. Of the 387 patients who had Hepatitis B reactivation, 304 were HBcAb (+)/HBs Ag (-) and 83 HBs Ag (+). The relative risk of hepatitis B reactivation was 5.52 in patients with HBcAb +ve when compared with the control population. This suggests that patients with HBcAb +ve are at a higher risk of hepatitis B reactivation when treated with rituximab [5].

Impact of prior hepatitis B immunity

Traditionally, hepatitis B surface antibody (anti-HBs) is protective in nature [3]. In 29 B cell lymphoma patients who were positive for anti-HBs before rituximab therapy, anti-HBs serologies before and after rituximab therapy were compared. Anti-HBs titers after rituximab treatment were significantly lower ($P < 0.001$) than those before treatment. None of the ten cases with pre-treatment anti-HBs titers above 100 mIU/ml became negative for anti-HBs after rituximab therapy. In contrast, 8 of the 19 patients with pre-treatment anti-HBs titers below 100 mIU/ml lost their anti-HBs. Of these, one patient developed HBs Ag seroconversion and HBV reactivation after rituximab therapy. Regarding patients with loss of anti-HBs or not, there was no significant difference in pre- and post-treatment immunoglobulin G levels between both groups. Pre-treatment anti-HBs titer is the only independent factor influencing the loss of anti-HBs [13] and might increase risk of hepatitis B reactivation in high risk patients.

The risk of hepatitis B reactivation after completion of immunochemotherapy

Preemptive lamivudine in lymphoma patients undergoing intensive chemotherapy can effectively prevent chemotherapy-related HBV reactivation in high risk patients (patients with HBs Ag positive or HBs Ag negative and HBV core antibody positive). Nevertheless, the safety profile after withdrawal of lamivudine and the long-term impact of rituximab-containing chemotherapy on HBV reactivation

has not been well defined. To illustrate the necessity of prolonged surveillance after cessation of preemptive lamivudine in lymphoma patients treated with rituximab and chemotherapy, four patients with B-cell NHL (and history of resolved hepatitis B) received R-CHOP. Preemptive lamivudine therapy was administered one week before chemotherapy until four weeks after completion of chemotherapy. Serial liver function tests and HBV-DNA levels were prospectively monitored. All patients studied prospectively had virological relapses with positive HBV-DNA 6-8 months after completion of R-CHOP therapy. Two of the three patients had biochemical relapses and one of them developed severe hepatitis. Sequencing for HBV polymerase gene in these patients failed to show emergence of lamivudine-resistant mutations. This suggests that delayed HBV reactivation can occur even after withdrawal of preemptive lamivudine [14]. Following completion of immunochemotherapy, antiviral prophylaxis is recommended to be continued for at least six months.

Do patients receiving chemotherapy alone need to be screened for hepatitis B reactivation?

The United States Centre for Disease Control and Prevention recommends pre-chemotherapy hepatitis B screening for all cancer patients, while the American Society of Clinical Oncology finds that there is insufficient evidence currently to support such a recommendation [15]. The risk of HBV reactivation in patients receiving chemotherapy was evaluated by Ling et al. [16] Patients receiving chemotherapy were divided into 4 categories patients received either doxorubicin based, carboplatin/gemcitabine, oxaliplatin or capecitabine chemotherapy. Thirty out of 448 (7%) screened patients were HBs Ag positive and 28 out of 30 received prophylactic antiviral therapy with no reactivation. Three out of 1149 patients overall (0.3%) developed HBV reactivation, all from the unscreened doxorubicin group. No unscreened patients in the other three treatment groups developed reactivation ($P < 0.001$). This data suggested patients receiving non-anthracycline based chemotherapy are at a lower risk for developing Hepatitis B reactivation [16].

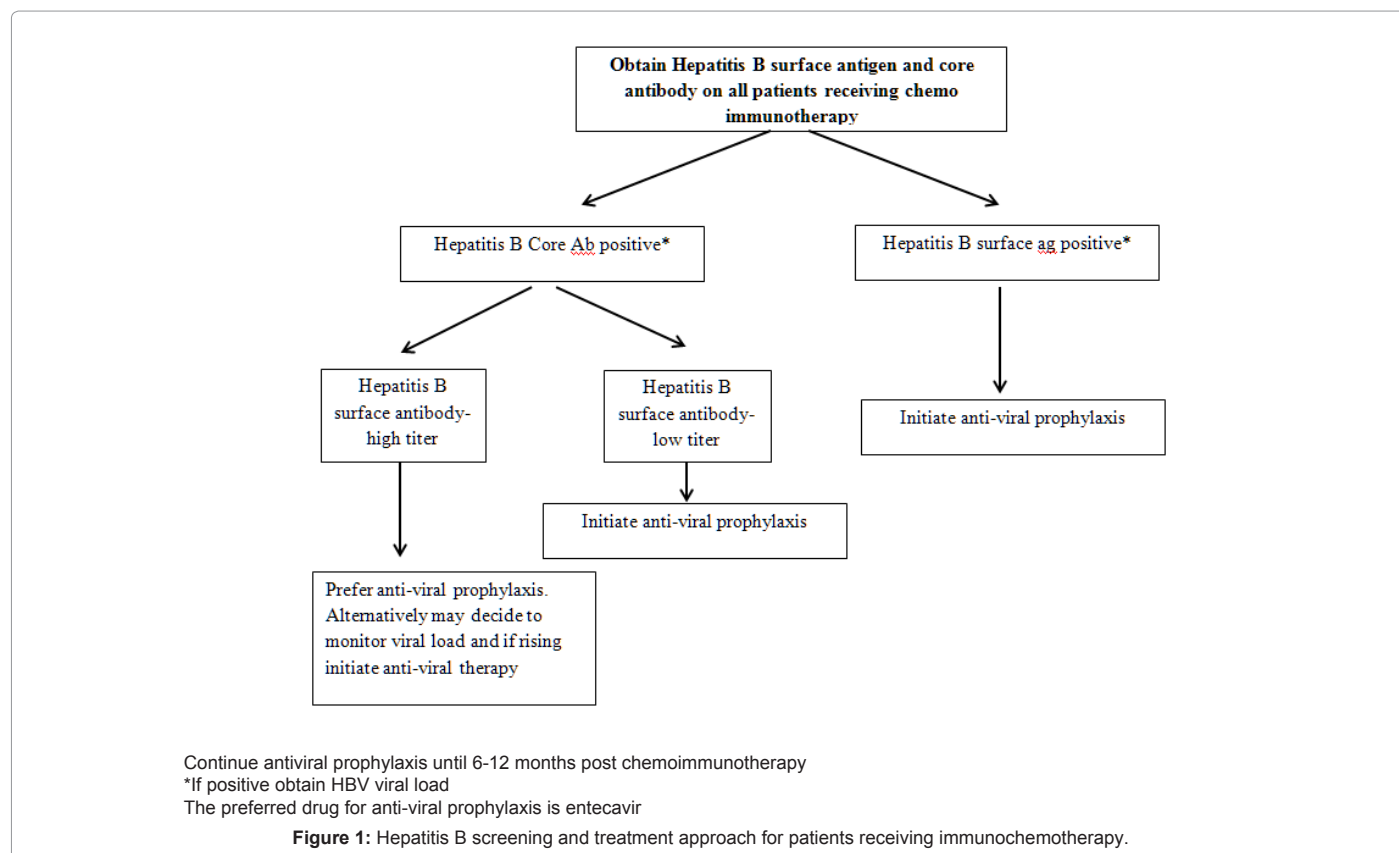
We recommend routine screening for hepatitis B in all patients receiving immunochemotherapy for hematological malignancies and suggested approach is summarized in Figure 1 and Table 1.

Prevention of Hepatitis B reactivation during Immunochemotherapy

Hepatitis B reactivation in patients receiving immunosuppressive

Drug	Dose	Resistance at one year	Side effects
Lamivudine	100 mg/day	15-30%	Lactic acidosis, hepatic steatosis, pancreatitis, lipodystrophy
Telbivudine	600 mg/day	6%	Lactic acidosis, hepatic steatosis, myopathy, peripheral neuropathy
Entecavir	0.5 mg/day (treatment naïve); 1 mg/day (Lamivudine-resistant virus)	None for treatment naïve; 7% if virus is Lamivudine-resistant	Lactic acidosis, hepatic steatosis, edema
Adefovir	10 mg/day	Minimal	Lactic acidosis, hepatic steatosis, weakness
Tenofovir	300 mg/day	None	Lactic acidosis, hepatic steatosis, renal toxicity, decreased bone mineral density

Table 1: Antiviral drugs for prevention of reactivation and treatment of hepatitis B.



therapy or chemotherapy may be associated with acute hepatitis, liver failure and/or death. Therefore it is crucial to screen patients and preventative measures such as close monitoring and anti-viral prophylaxis need to be considered.

Lamivudine, 100 mg/d, was given orally in a pilot study of 20 patients from initiation until a month after the end of chemotherapy, which included corticosteroids and/or purine analogues in 85% of cases. It was well tolerated and did not cause any unexpected reduction of cytostatic drugs dosages. HBV-DNA levels decreased in six out of six patients. Two patients developed transient hepatitis. HBV reactivation was documented in only one of these patients who had stopped lamivudine one month before. Thus, primary prophylaxis with lamivudine is well-tolerated and serves as an effective method in reducing the frequency of chemotherapy-induced HBV reactivation in chronic HBs Ag carriers [17].

Selection of Initial Antiviral Agent (HBs Ag Positive and anti-HBV Core Antibody Positive)

The efficacy of entecavir as compared with lamivudine for the prophylaxis of HBV reactivation in patients with hematological disease receiving immunosuppression or chemotherapy was evaluated. Patients treated for hematological disease with pretreatment serological evidence of chronic hepatitis B (CHB) (HBs Ag positive) or resolved HBV infection (HBs Ag negative but HBV core antibody positive) were included in this study. Patients received lamivudine 100 mg or entecavir 0.5 mg daily. HBV reactivation defined as a one log increase in HBV DNA from baseline or reversion to HBs Ag positivity was evaluated. Of the 40 patients included in the study, 65% (4 CHB and 22 resolved HBV) received entecavir and 35% (11 CHB and 3 resolved HBV)

received lamivudine. One patient with resolved HBV experienced HBV seroconversion related to premature cessation of entecavir. Eight patients with CHB had detectable HBVDNA levels at baseline; one case of HBV reactivation related to probable lamivudine resistance was identified. No HBV related deaths occurred [18]. Generally, lamivudine and entecavir are both efficacious in the prophylaxis of hepatitis B reactivation (Table 1). However, entecavir should be used in preference to lamivudine in patients CHB with detectable baseline HBV DNA levels. This has recently been confirmed by a prospective analysis comparing the efficacy of prophylactic entecavir and lamivudine in preventing hepatitis B reactivation in Hbs Ag-positive patients with untreated Diffuse Large B Cell Lymphoma (DLBCL) under R-CHOP treatment. Patients with low serum HBV DNA levels were randomized to receive entecavir or lamivudine during R-CHOP treatment and for 6 months after completion of immunochemotherapy. A total of 229 patients were included in this study. Compared with the lamivudine group, the entecavir group had significantly lower rates of hepatitis (8.2% vs. 23.3%, $P=0.022$), HBV reactivation (6.6% vs. 30.0%), delayed HBV-related hepatitis (0 vs. 8.3%) [19]. Therefore, entecavir is the recommended prophylactic antiviral agent of choice.

Summary of Screening and Treatment Guidelines for Patients undergoing Immunochemotherapy for Hematological Malignancies

Summary of screening and treatment guidelines are outlined in (Figure 1).

At minimum the screening panel should include tests for HBV surface antigen (HBs Ag), HBV core antibody (anti-HBc), and the HBV surface antibody (anti-HBs). All patients with a positive HBs

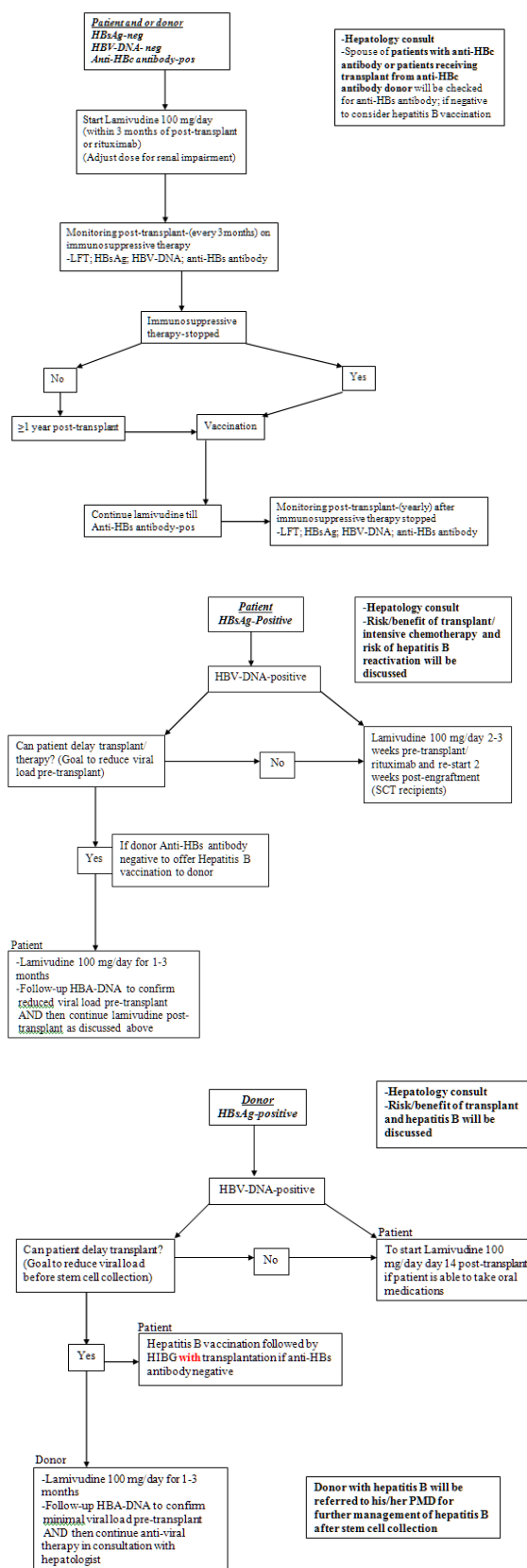


Figure 2: Suggested approach to prevent HBV reactivation in patients receiving immunochemotherapy and allo-SCT recipients.
- Lamivudine can be replaced by another drug (summarized in Table 2) in consultation with hepatology and or infectious disease team.

Ag or anti-HBc should undergo further screening with an HBV DNA assay to detect viremia [6,20,21].

Prophylactic antiviral therapy is recommended for patients with HBs Ag-positive and receiving immunochemotherapy. In patients with HBc Ab positivity and HBs Ag-negative, prophylactic antiviral therapy is preferred; however, in patients with a concurrent high-level hepatitis B surface antibody, these patients may be monitored with serial hepatitis B viral load. Viral titers should be monitored monthly and any indication of rising viral load or development of LFT abnormalities should prompt consultation with hepatology.

Hepatitis B Reactivation after Allogeneic Stem Transplantation

Patients previously infected with HBV undergoing an allograft and recipients from HBV carrier donors are at risk of post transplant viral reactivation. HBV reactivation after allo-SCT is a well-known complication not only in HBs Ag carriers, but also in patients with resolved HBV infection. [4,6,22-24]. The frequency of HBV-RS is reported to be in the range of 14%-50% after allo-SCT (median time 6-72 months). Variations may be attributable to different immunosuppressive regimens or different incidence and severity of chronic GVHD. The presence of chronic GVHD may result in earlier onset of RS. These results emphasize the need for continued monitoring for HBV RS in patients at risk, especially those receiving prolonged immunosuppressive therapy [4,6,20,25,26].

Risk factors for reactivation and exacerbation of HBV replication in HCT recipients include treatment with high-dose steroids, fludarabine/rituximab, or alemtuzumab and also theoretical higher risk in cord blood and mismatched related or unrelated donor allo-SCT. Clinical hepatitis may become further exacerbated during immune recovery and discontinuation of immunosuppression [20].

Evaluation, Post-SCT Course, Management and Follow-up

Pre-SCT evaluation

Due to the risk of reactivation and donor-derived infection after SCT, all candidates for allo-SCT and their donors should be screened for HBV. The screening panel should include tests for HBV surface antigen (HBs Ag), HBV core antibody (anti-HBc), and the HBV surface antibody (anti-HBs). All patients with a positive HBs Ag or anti-HBc should undergo further screening with an HBV DNA assay to detect viremia [6,20,21].

Influence of donor immunity

Stem cell donors who have developed natural immunity to hepatitis B may adoptively transfer this immunity to actively infected recipients, who may then clear that infection more easily after transplantation [27]. Hui et al. demonstrated sustained clearance of HBs Ag and seroconversion to anti-HBs positivity in 64.5% of recipients who received stem cells from donors with natural immunity [28]. All of these stem cell recipients also received antiviral therapy against HBV- usually lamivudine. None of the HBV-infected recipients who received stem cells from donors who were anti-HBc negative cleared the infection after transplantation. This experience demonstrates that one should always attempt to find a hepatitis B immune donor (post-vaccination or natural immunity) for any recipient who is actively infected or recipients with resolved HBV infection. In a scenario where this is not possible, patients should receive nucleoside analogues with

their conditioning regimen. Patients lacking antibodies to HBV who are to receive a graft from a HBs-Ag positive donor, if possible should be vaccinated prior to HSCT. It is also recommended that they receive hepatitis B immunoglobulin in combination with lamivudine [29].

Immunizing HBV naive patients

If feasible, HBV naive patients should be vaccinated before transplantation. The traditional vaccination schedule includes three doses of vaccine at 0, 1, and 6 months. Every attempt should be made to immunize with at least 2 doses prior to allo-SCT, given at least 3-4 weeks apart. The final dose can be given after SCT. Delaying the third dose up to 1 year after the first dose may actually lead to an increase in the anti-HBs levels as significant immune recovery will have occurred by then in most patients [2,20]. Anti-HBs levels should be checked one month after completion of the series. If no seroconversion has occurred, repeat vaccination should be attempted. Following autologous or allogeneic stem cell transplantation, patients with hepatitis B negative markers (including those vaccinated before HSCT) should receive the three doses of vaccine starting at 6 months after HSCT [29,30].

Management of HBV-infected transplant recipients based on pre-transplant status

Transplant recipient with active infection (HBs Ag positive): Historically, patients who were HBs Ag positive before transplantation had a high risk of post-transplant liver disease. In a long-term follow-up of 82 HBsAg positive stem cell recipients from one institution, 19.5 % had developed hepatitis and 10% had progressed to cirrhosis [28]. None of the 20 patients who cleared their virus went on to develop cirrhosis. Viral reactivation and hepatitis occurred as late as 10 years after transplantation.

There are numbers of drugs with proven efficacy against HBV has expanded in recent years (Table 1). Current guidelines from the American Association for the Study of Liver Diseases recommend treatment for at least 6 months after completion of chemotherapy or immunosuppressive therapy, but no specific guidelines exist for SCT recipient (our suggested approach summarized in Figure 2).

Due to the degree of immunosuppression and the possible delay of immune recovery in these allo-SCT recipients, duration of antiviral therapy of at least 12 months after cessation of immunosuppression is preferred [21] Lamivudine (100 mg/day) is well tolerated and has been the antiviral compound most used in stem cell recipients. However, resistance to lamivudine occurs in 15-30% of patients on prolonged usage. Patients being treated with lamivudine need to be carefully monitored for viral breakthrough [3]. The two newer antiviral agents that are most often recommended are entecavir (0.5 mg/day) and tenofovir (300 mg/day) (Table 1). Both are associated with a very low rate of resistance development, but are more expensive. Entecavir has few side effects. Tenofovir carries a low risk of renal toxicity which can complicate management in allo-SCT recipients who are on calcineurin inhibitors.

Transplant recipients with resolved infection (HBsAg negative, anti-HBc positive, anti-HBs positive): These patients have resolved their hepatitis B infection and have serological evidence of natural immunity to the virus but are at risk for reactivation, which increases steadily over time. There does not appear to be any date beyond which one can be sure that reactivation will not occur. These recipients should be followed with assays for HBs Ag, viral DNA and liver function testing every 2-3 months. Based on recent data, these patients should receive pre-emptive therapy to prevent reactivation (lamivudine

preferred initially). Patients who develop a detectable viral load should be initiated on antiviral treatment (entecavir or other drug preferred) with continuation of monitoring as with the HBs Ag positive group.

Transplant recipients with indeterminate infection (anti-HBc positive but negative for HBs Ag and anti-HBs): This serological profile can represent one of three states: occult infection, past resolution of infection with a waning antibody titer to HBs Ag, or a false positive anti-HBc with no prior or current infection (e.g. rarely seen after intravenous immunoglobulin). Some authorities recommend repeating the serological tests after giving a booster dose of the HBV vaccine as a brisk rise in anti-HBs in response to the vaccine usually indicates that the patient has true past infection with underlying natural immunity [2]. An HBV DNA assay should be obtained in all patients with this profile. If the DNA assay is positive for circulating hepatitis B virus, antivirals should be administered with serial monitoring of the antiviral response. If the viral DNA assay is negative, our approach is to manage the patient prophylactically with antiviral medications till off immunosuppressive therapy and have developed immunity to hepatitis B-vaccination (Figure 1).

Complications from hepatitis B virus infection following allo-SCT

The risk for adverse outcomes from hepatitis B infection is most marked in patients going into transplantation with active infection as denoted by positive tests for HBs Ag. Prior to the availability of antiviral therapy, hepatitis occurred in >50% of such patients. Effective antiviral prophylaxis has decreased this risk to 0-9% [2,31]. The mean time to HBV reactivation (defined as a >2-fold rise in ALT) is 4 months in patients who do not receive prophylaxis and the associated mortality rate has varied from 5-40% in different case series [2,21,31].

Identified risk factors for RS include extensive chronic GVHD, low pre-transplant anti-HBs titers, multiple prior chemotherapy regimens, and a diagnosis of chronic hematological disease [2,4,24]. Biochemical or clinical hepatitis is reported in the majority of patients with RS [4,22]. Fulminant hepatitis and death from liver failure can occur when the patients recovering immune systems recognize the reappearing viral antigens. Fortunately, the occurrence of severe hepatitis has become uncommon since the availability of antiviral therapy.

No evidence links chronic HBV infection to an increased risk of veno-occlusive disease in the absence of underlying cirrhosis. One study performed prior to widespread use of prophylactic or preemptive antiviral therapy showed that patients who were HBs Ag positive before transplantation had an increased incidence of acute GVHD [31]. Not surprisingly, these patients were also significantly more likely to develop cirrhosis (8/82) than stem cell transplant controls (0/721) without hepatitis B infection [28,32].

Conclusion

Reverse seroconversion of hepatitis B virus after immunochemotherapy or allo-SCT is a significant long-term complication in patients with history of resolved HBV infection. Published data emphasize the importance of prophylaxis with antiviral agents (e.g. lamivudine), hepatitis B vaccine, long-term hepatitis B serologic monitoring, and prompt initiation of effective anti-viral treatment if HBV-RS occurs.

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